Pomalidomide for multiple myeloma – third line

SUMMARY

Pomalidomide (CC-4047) is intended to be used in combination with dexamethasone as third line treatment for relapsed and/or refractory multiple myeloma (MM) in patients who have received treatment with both lenalidomide- and bortezomib-containing regimens. If licensed, pomalidomide will offer an alternative treatment option for these patients. Pomalidomide is an immunomodulatory drug analogue of thalidomide. It has demonstrated greater activity than thalidomide \textit{in vitro} and it may also inhibit the destructive effects of MM in the bone microenvironment by inhibiting osteoclast differentiation.

In 2009, 4,270 people were diagnosed with MM in England and Wales, giving a crude incidence rate of 8 per 100,000 population. Median survival for MM is approximately 3 to 5 years\(^1\), though this can increase to a median 7 years with use of intensive therapy.

Induction therapy followed by high-dose melphalan and autologous stem cell transplantation is primarily offered to MM patients less than 65 years of age, and provides the greatest chance of prolonged survival and complete remission. In older patients combination therapy is usually given, with a treatment regimen which is patient specific, dependent on age, and may include: melphalan, prednisolone and thalidomide; cyclophosphamide, dexamethasone and thalidomide; or bortezomib, melphalan and prednisolone. There are currently no standard third-line therapies for patients with MM, however NICE guidance recommends bortezomib after first relapse and lenalidomide at second or later relapse. Pomalidomide in combination with low-dose dexamethasone is currently in a phase III clinical trial comparing its effect on disease progression with high-dose dexamethasone alone. This trial is expected to complete in May 2013.
TARGET GROUP

- Multiple myeloma (MM): relapsed and/or refractory – third or subsequent line; in combination with dexamethasone; patients who have received treatment with both lenalidomide- and bortezomib-containing regimens.

TECHNOLOGY

DESCRIPTION

Pomalidomide (CC-4047) is an immunomodulatory drug analogue of thalidomide (IMiD)\(^2\). It is intended as a treatment for relapsed and/or refractory MM in patients who have received treatment with both lenalidomide- and bortezomib-containing regimens. MM is characterized by accumulation of malignant plasma cells in the bone marrow, bone lesions, and immunodeficiency\(^3\). IMiDs may disrupt stromal support for MM-cells by down regulating the expression of adhesion molecules\(^4\); have antineoplastic and apoptotic effects through blockade of nuclear factor-κB and the caspase-8/death receptor pathway signalling\(^5\); and overcome conventional drug resistance by down-regulating immunosuppressive cytokines, augmenting the proliferation and activation of T lymphocyte and natural killer cells\(^2,3\). IMiDs also down regulate vascular endothelial growth factor and beta fibroblast growth factor, inhibiting angiogenesis\(^3\). Pomalidomide appears to display equivalent anti-angiogenic activity to thalidomide, however it exhibits increased stimulation of apoptosis via the inhibition of cellular COX-2 production (a predictor of poor outcome)\(^6\), increased anti-inflammatory effects via the inhibition of TNF-alpha production\(^1\), and a much enhanced stimulation and activation of the immune response\(^2,3\).

Pomalidomide is administered orally at 4mg once daily on days 1–21 of a 28 day cycle in combination with dexamethasone orally at 40mg once daily on days 1, 8, 15 and 22.

Pomalidomide is in phase III clinical trials for the treatment of idiopathic myelofibrosis.

INNOVATION and/or ADVANTAGES

If licensed, pomalidomide will offer an alternative treatment option for patients with relapsed and/or refractory MM. Pomalidomide has demonstrated greater activity than thalidomide \textit{in vitro} and it may also inhibit the destructive effects of MM in the bone microenvironment by inhibiting osteoclast differentiation\(^7\).

DEVELOPER

Celgene.

AVAILABILITY, LAUNCH OR MARKETING

Pomalidomide is a designated orphan drug in the EU. It is in phase III clinical trials.
MM develops from plasma cells in the bone marrow and is the 17th most common cancer in the UK\(^8,9\). The uncontrolled over-production of abnormal plasma cells in MM results in the production of a large amount of a single type of abnormal antibody, and a reduction in the number of normal white cells, red cells and platelets\(^8\). This leads to anaemia, repeated infections, bone pain, hypercalcaemia, kidney damage, tiredness and weight loss\(^8,10\).

NICE Guidance

- NICE technology appraisal in development. Bortezomib for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation for the treatment of multiple myeloma (ID610). Expected October 2013\(^21\).

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\(^a\) Expert personal opinion.
• NICE technology appraisal in development. Lenalidomide for the treatment of newly diagnosed multiple myeloma (ID474). Suspended July 201222.
• NICE technology appraisal in development. Lenalidomide for the maintenance treatment of multiple myeloma after autologous stem cell transplantation (ID475). Suspended July 201223.
• NICE technology appraisal in development. Bortezomib for consolidation therapy after autologous stem cell transplantation for the treatment of multiple myeloma (ID529). Expected May 201224.
• NICE technology appraisal in development. Multiple myeloma (one prior therapy) – vorinostat (with bortezomib) (ID501). Suspended May 201225.
• NICE technology appraisal. Bortezomib and thalidomide for the first line treatment of multiple myeloma (TA228). 200728.
• NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). 200927.
• NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). 200728.
• NICE Cancer Service guideline. Improving outcomes in haemato-oncology cancer (CSGHO). 200329.

Other Guidance


EXISTING COMPARATORS and TREATMENTS

Induction therapy followed by high-dose melphalan and autologous stem cell transplantation (ASCT) provides the greatest chance of prolonged survival and complete remission; however this typically only improves survival by up to a year13,b. This treatment is also limited to patients who are able to tolerate it; in Europe, ASCT is primarily offered to patients under 65 years of age30. As the median age at diagnosis is 70 years, more than 50% of newly diagnosed MM patients are likely to be ineligible for this therapy. The aim in such patients is to give effective combination therapy. The treatment regimen will be patient specific and dependent on age and may include melphalan, prednisolone and thalidomide; cyclophosphamide, dexamethasone and thalidomide; or bortezomib, melphalan and prednisolone31. There are currently no standard third-line therapies for patients with MM, however NICE guidance27 recommended bortezomib after first relapse and lenalidomide at second or later relapse13,c.

Efficacy and Safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NIMBUS, NCT01311687, CC-4047-MM-003, 2010-019820-30; pomalidomide in combination with low-dose dexamethasone vs high-dose dexamethasone; phase III.</th>
<th>NCT01324947, CC-4047-MM-003/C, 2010-023343-16; pomalidomide; phase III extension study.</th>
<th>STRATUS, NCT01712789, CC-4047-MM-010, 2012-001888-78; pomalidomide in combination with low-dose dexamethasone; phase III.</th>
</tr>
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</table>

b Expert personal opinion.
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<tr>
<th>Information</th>
<th>Manufacturer</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada, Russia and Australia.</td>
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<tr>
<td>Participants</td>
<td>n=426; aged ≥18 years; MM; refractory or relapsed; ≥2 consecutive cycles of prior treatment that included lenalidomide, bortezomib and alkylating agent; failed treatment with lenalidomide and bortezomib.</td>
<td>n=85 (planned); aged ≥18 years; subjects who were enrolled in NCT01311687 and discontinued study therapy with dexamethasone alone after disease progression.</td>
<td>n=507 (planned); aged ≥18 years; MM; refractory or relapsed; ≥2 consecutive cycles of prior treatment that included lenalidomide and bortezomib either alone or in combination regimens.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to pomalidomide 4mg, orally on days 1-21 of a 28-day cycle in combination with dexamethasone 20mg (for subjects &gt;75 years of age) or 40mg (for subjects ≤75 years of age) orally once daily on days 1, 8, 15, and 22 of a 28-day cycle; or dexamethasone 20mg (for subjects &gt;75 years of age) or 40mg (for subjects ≤75 years of age) orally once daily on days 1-4, 9-12 and 17-20 of a 28-day cycle.</td>
<td>Pomalidomide 4mg orally on days 1-21 of a 28-day cycle.</td>
<td>Pomalidomide 4mg, orally on days 1-21 of a 28-day cycle in combination with dexamethasone 20mg (for subjects &gt;75 years of age) or 40mg (for subjects ≤75 years of age) orally once daily on days 1, 8, 15, and 22 of a 28-day cycle.</td>
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<td>Follow-up</td>
<td>Active treatment until disease progression. Follow-up for up to 5 years.</td>
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<tr>
<td>Primary outcome</td>
<td>Time to disease progression or death.</td>
<td>Response based on the IMWG uniform response criteria.</td>
<td>AEs.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Adverse events (AEs), survival, response according to IMWGc uniform response criteria, response according to EBMTd criteria, time to progression (TTP), time to IMWG or EBMT response, time from response to disease progression, time to increased haemoglobin (Hb), time to improvement of bone pain, time to improvement of renal function, time to improvement of ECOGe.</td>
<td>Response based on EBMT criteria, AEs, survival, time to disease progression based on IMWG or death, time from response to disease progression.</td>
<td>Overall response rate (ORR), time to response, duration of response (DoR), progression-free survival (PFS), TTP, OS.</td>
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* International Myeloma Working Group.  
* European Group for Blood and Marrow Transplantation.  
* Eastern Cooperative Oncology Group.
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<tr>
<th><strong>Expected reporting date</strong></th>
<th>Study completion date reported as May 2013.</th>
<th>Study completion date reported as Jun 2013.</th>
<th>Nov 2019.</th>
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**Trial**

- **NCT00558896, CDR0000574742, P30CA15083, 07-003064, NCI-2009-01283, MC0789; pomalidomide in combination with dexamethasone; phase II.**
- **NCT01053949, IFM2009-02, 2009-013319-36, 2009_28/0924; pomalidomide in combination with dexamethasone; phase II.**

**Sponsor**

- Mayo Clinic.
- University Hospital, Lille.

**Status**

- Ongoing.
- Ongoing.

**Source of information**

- Publication4,35, abstract36, trial registry37, manufacturer.
- Abstract38,39, trial registry40, manufacturer.

**Location**

- USA.
- France.

**Design**

- Non-randomised.
- Non-randomised.

**Participants**

- n=258 (planned); aged ≥18 years; MM; refractory to lenalidomide and bortezomib.
- n=84; aged ≥18 years; MM; symptomatic and progressive following lenalidomide and/or bortezomib treatment.

**Schedule**

- Randomised to pomalidomide 2mg or 4mg, both orally on days 1-28, in combination with dexamethasone 40mg orally on days 1, 8, 15, and 22 of a 28-day cycle.
- Randomised to pomalidomide 4mg on days 1-21 or on days 1-28, both orally in combination with dexamethasone 40mg orally on days 1, 8, 15, and 22 of a 28-day cycle.

**Follow-up**

- Active treatment until disease progression. Follow-up for 6 months.
- Active treatment until disease progression. Follow-up for 6 months.

**Primary outcomes**

- Complete response (CR), partial response (PR), or very good partial response (VGPR).
- Response rate.

**Secondary outcomes**

- Toxicity, duration of remission.

**Key results**

- **Pomalidomide 2mg (n=35):** CR, 0%; VGPR, 14%; PR, 11%; minor response (MR), 23%; overall response (OR), 49%; OS at 6 months, 78% (95% CI, 65-94); PFS at 6 months, 56% (95% CI, 41-75).
- **Pomalidomide 4mg (n=35):** CR, 3%; VGPR, 9%; PR, 17%; MR, 14%, OR, 43%; OS at 6 months, 67% (95% CI, 52-86); PFS at 6 months, 34% (95% CI, 21-55).

**Adverse effects (AEs)**

- Myelosuppression was the most common toxicity. Grade 3 or 4 haematological toxicity possibly attributable to treatment.

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1 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Multiple Myeloma.
2 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Cancer.
3 European Quality of Life-5 Dimensions.
| Occurred in 71% of 2mg cohort and 74% of 4mg cohort. Pomalidomide 2mg (n=35): Grade 3-4 myelosuppression: neutropenia (29%), thrombocytopenia (3%), and anaemia (9.6%). Grade 3-4 non-haematologic toxicities: overall (16%); pneumonitis (3%), hyperglycaemia (3%), renal failure (3%), fatigue (3%), and thrombosis (3%). | Expected reporting date | Primary completion date reported as Sep 2012. Study completion date reported as Aug 2013. |

| Trial | NCT00833833, CC-4047-MM-002; pomalidomide vs pomalidomide in combination with low-dose dexamethasone; phase II. |
| Sponsor | Celgene Corporation. |
| Status | Ongoing. |
| Source of information | Abstract [41,42,43], presentation [44], trial registry [45], manufacturer. |
| Location | USA and Canada. |
| Design | Randomised, active-controlled. |
| Participants | n=221; aged ≥18 years; relapsed and refractory MM; prior treatment with ≥2 cycles of lenalidomide and ≥2 cycles of bortezomib (either in separate regimens or within the same regimen). |
| Schedule | Randomised to pomalidomide 4mg on days 1-21; or pomalidomide 4mg on days 1-21 in combination with dexamethasone 40mg on days 1, 8, 15, and 22 of a 28-day cycle. All given orally. Subjects who progress in the pomalidomide only arm crossover to the combination arm. |
| Follow-up | Active treatment until follow up for survival. |
| Primary outcome | PFS. |
| Secondary outcomes | Objective response using EBMT criteria, time to response, DoR, OS, AEs, response using IMWG uniform response criteria, relationship between response and cytogenetic abnormalities. |
| Key results | Pomalidomide (n=108) vs pomalidomide with dexamethasone (n=113): At least PR, 9% vs 30%; at least MR, 25% vs 45%; SD, 46% vs 35%; progressive disease, 16% vs 6%; median DoR, not reached (NR) vs 7.4%; median time to response in subjects with at least PR, 2.0 vs 1.9 months; median PFS, 2.5 months vs 3.8 months (p=0.037, hazard ratio (HR) = 0.73); median OS, 13.6 months vs 14.4 months (p=0.449, HR = 0.85). Pomalidomide with dexamethasone group only: Lenalidomide and bortezomib refractory subset (n=69): at least PR, 28%; at least MR, 46%; SD, 35%; time to at least PR, 1.8 months; median DoR in subjects with at least PR, 6.2 months; median DoR in subjects with MR, 3.0 months; median PFS, 3.8 months; 1-year survival, 61%; OS, 13.5 months. Lenalidomide and bortezomib refractory with prior BM transplant subset (n=47): at least PR, 34%; at least MR, 53%; SD, 28%; time to at least PR, 1.6 months; median DoR in subjects with at least PR, 5.7 months; median DoR in subjects with MR, 5.7 months; median PFS, 4.6 months; 1-year survival, 67%; OS, NR. |
| Adverse effects (AEs) | Overall grade 3 or 4 AEs Pomalidomide (n=107) vs pomalidomide with dexamethasone (n=112): Neutropenia, 47% vs 38%; thrombocytopenia, 22% vs 19%; anaemia, 22% vs 21%; leukopenia, 6% vs 10%; pneumonia, 14% vs 19%; fatigue, 10% vs 10%; back pain, 12% vs 9%; dyspnoea, 7 vs 13%. |
ESTIMATED COST and IMPACT

COST

The cost of pomalidomide is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Other:
- Reduced symptoms or disability
- No impact identified

Impact on Services

- Increased use of existing services
- Re-organisation of existing services
- Other:
- Decreased use of existing services
- Need for new services
- None identified

Impact on Costs

- Increased drug treatment costs
- Other increase in costs:
- Reduced drug treatment costs
- Other reduction in costs:
- None identified

Other Issues

- Clinical uncertainty or other research question identified:
- None identified

REFERENCES


43 Richardson PG, Siegel DS, Vij R et al. Randomized, open label phase 1/2 study of pomalidomide (POM) alone or in combination with low-dose dexamethasone (LoDex) in patients (pts) with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide (LEN) and bortezomib (BORT): phase 2 results. 53rd American Society of Hematology Annual Meeting and Exposition. December 2011. San Diego, California, USA. Abstract 634.